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A Convenient Synthesis of Some Diarylurea and Thiourea Derivatives as Antimicrobial Compounds

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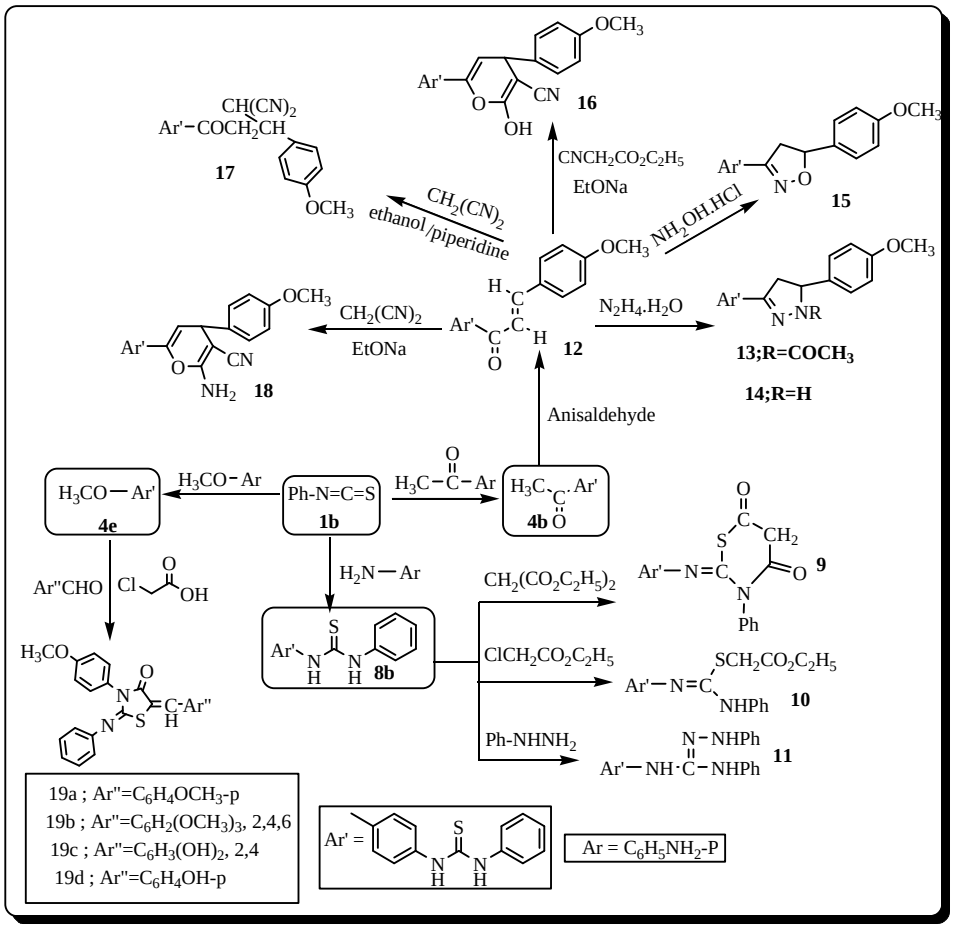


Abstract

A simple and efficient method has been developed for the synthesis of unsymmetrical 1,3-diarylurea and thiourea derivatives (**3 and 4**) from phenylisocyanate or phenylisothiocyanate with various aromatic amines. Unsymmetrical bis-diarylthiourea derivative **(8b)** reacted with diethyl malonate, ethyl chloroacetate and phenyl hydrazine, while **(12)** reacted with hydrazine hydrate, hydroxylamine hydrochloride, ethyl cyanoacetate and malononitrile. All compounds are characterized by I.R, ^{1}H-NMR, ^{13}C-NMR and MS spectral data. A comparison of synthesis of the products by conventional method and by microwave has also been undertaken. The screened antibacterial activity of the products has been recognized.

Keywords: Phenylurea, Phenylthiourea, Thiazolidine, Microwave, One pot reaction, Antimicrobial activity

1. Introduction

Unsymmetrical 1,3-diarylureas have attracted much attention due to their diverse applications in agriculture, medicine, petrochemicals, supra-molecular chemistry(anion receptors),biology and as important intermediates and bifunctional organo-catalysts in organic synthesis (Amendola *et al*. 2010; Lang *et al*.2012; Kim *et al*.2006). 1,3-Diarylurea derivatives including pyridine moiety have shown different biological activities, namely as antitumor agents (Hayakawa *et al*.2004) and receptor tyrosine kinase inhibitors (Heyman *et al*.2007).Moreover,

3-[3-(2-bromophenyl)ureido]-6-chloro-2-hydroxy-N,N-dimethylbenzene- sulfonamide and 1-[4-(1-oxoisoindolin-4-yl)phenyl]-3-[4-(trifluoromethyl)phenyl]urea were prepared and applied as antagonist for the CXCR2 chemokine receptor (Jin *et al*.2004) and KDR kinase inhibitor (Curtin *et al*.2004), respectively. On the other hand, diarylureas, e.g., Sorafenib was used as a potential antiproliferative agent against skin cancer, melanoma and renal cell cancers (El Gamal *et al*.2011). Also, N-(4-tert-butylphenyl)-N'-(2-chloroethyl)urea showed potent anticancer activity (Mounetou *et al*.2001; Mounetou *et al*.2003); 1-(5-oxo-5H-pyrrolo[2,1-a]isoindol-9-yl)-3-(pyridin-2-yl)urea has proved to be one of a new class of potent cdk4 inhibitors (Honma *et al*.2001); diuron was used as a herbicide (Proctor *et al*.2002);1-[3-(4-chlorophenoxy)phenyl]-3-(3,4-dichlorophenyl)urea and1,3-bis(3,4-dichlorophenyl)-urea showed antibacterial activity (Proctor *et al*.2002).

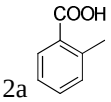
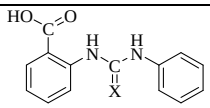
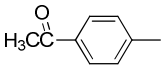
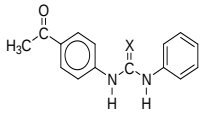
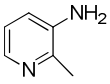
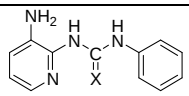
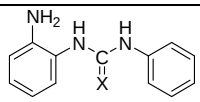
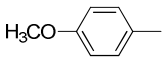
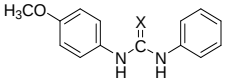
2. Results and discussion

The extensive biological activity of diarylurea derivatives (Miyazaki *et al*. 2007; Ávalos *et al*. 2005; Peixoto *et al*. 2012) prompted us to conveniently synthesize a new series of this family. Reflux of phenylisocyanate **1a** or phenylisothiocyanate **1b** with aromatic amines **2a-f** in absolute ethanol gave the corresponding monoadduct diarylureas **3a-e** and diarylthioureas **4a-e**, respectively in good yields.

Ph-N=C=X + NH_2Ar → PhNH-CX-NHAr

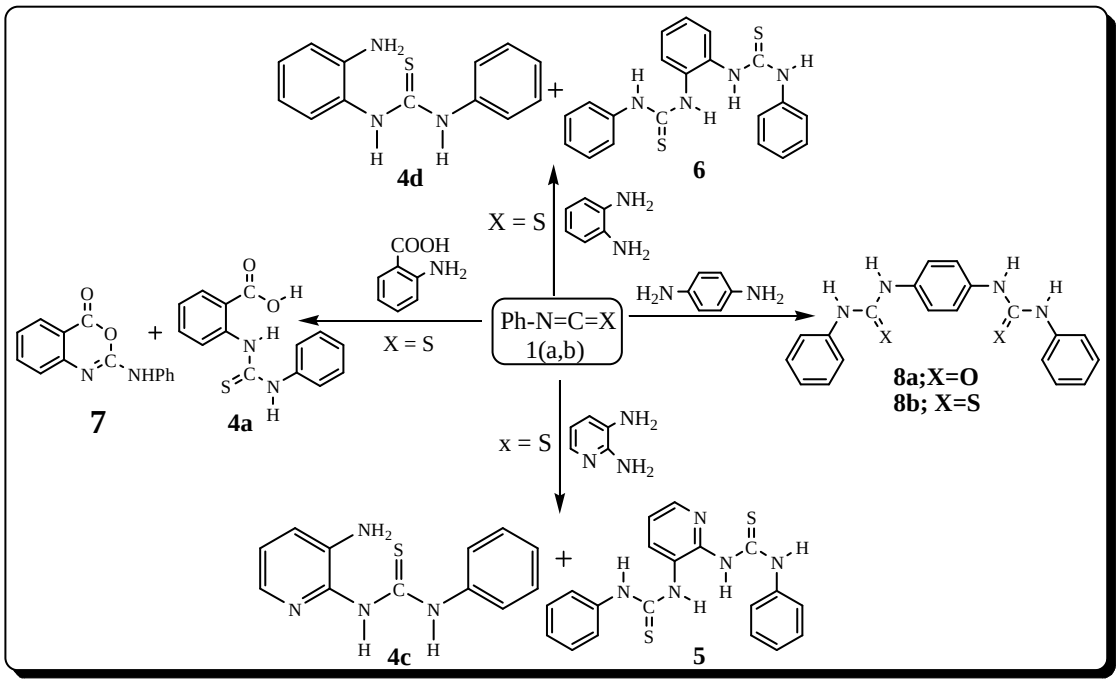
1a; X=O 1b; X=S 2a-e 3a-e; X=O 4a-e; X=S

Table (1)

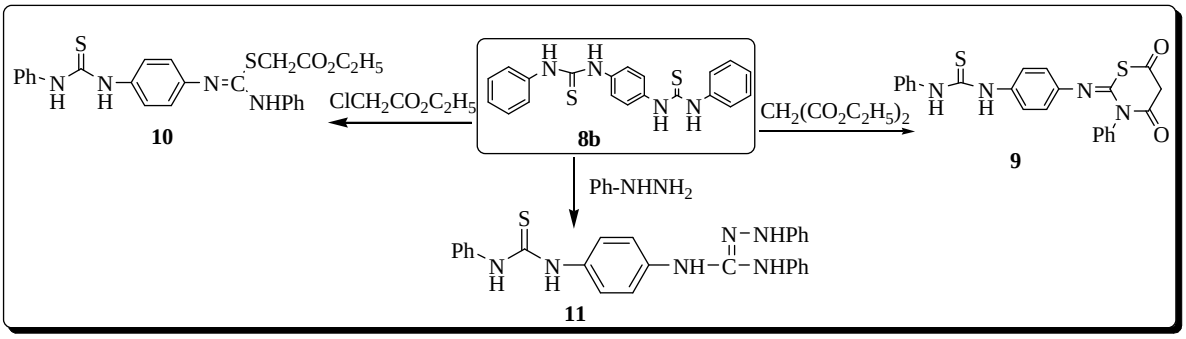
Ar	Reaction products
2a 	3a,4a 
2b 	3b,4b 
2c 	3c,4c 
2d 	3d,4d 
2e 	3e,4e 

In case of formation of **4a**, **4c** and 4d another products **7**,**5** and **6** were also isolated. Formation of compounds **7** can be explained through rearrangement of the monoadduct **4a** to the thiol form, followed by elimination of one molecule of H_2S, while the diadduct compounds **5** and **6** are formed through addition of another molecule of phenylisothiocyanate to the monoadduct compounds **4c** and **4d** respectively.

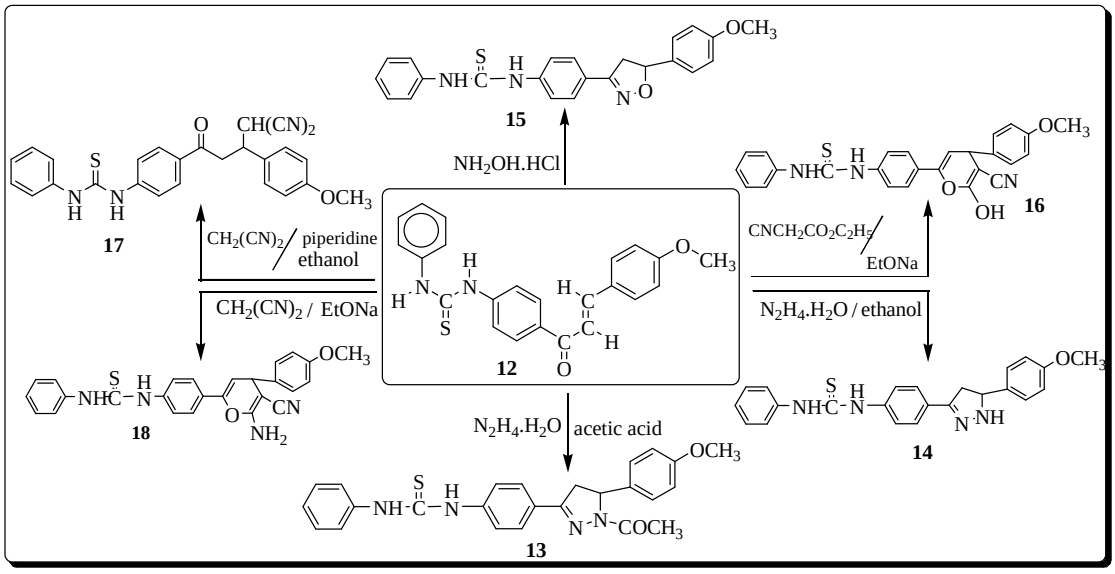
Interestingly, reaction of p-phenylenediamine **2f** with phenyl isocyanate **1a** and phenyl isothiocyanate **1b** the diadduct **8a** and **8b** was obtained, respectively.



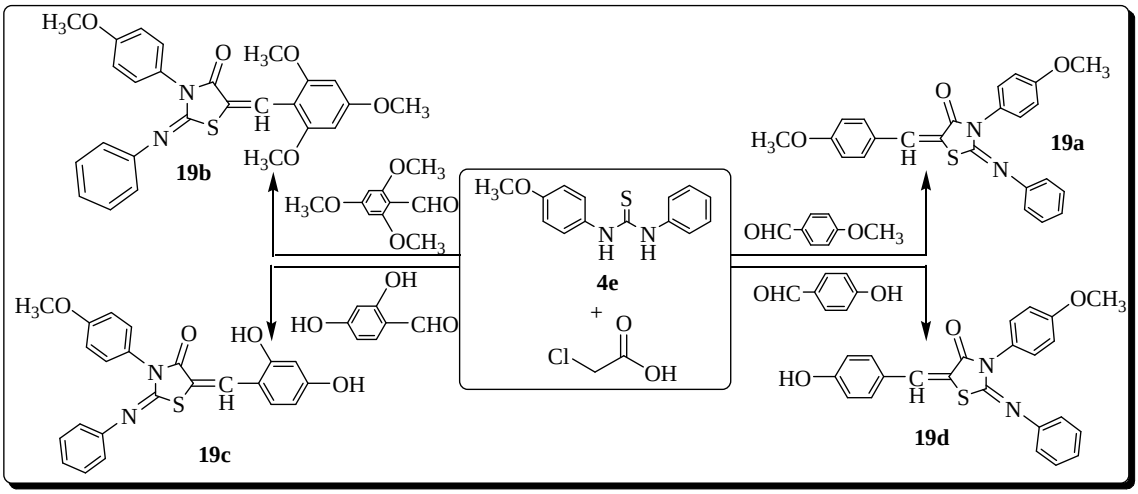
Fusion of **8b** with diethyl malonate gave 1-(4-(4,6-dioxo-3-phenyl-1,3-thiazinan-2-ylideneamino)phenyl)-3-phenylthiourea **9**, while its reaction with ethyl chloroacetate in DMF/K_2CO_3 gave ethyl 2-(N-phenyl-N'-(4-(3-phenylthioureido)phenyl)carbami-midoylthio)acetate **10**, through rearrangement of **8b** to the thiol form followed by elimination of two molecules of ethanol and one molecule of HCl to obtain compounds **9** and **10**, respectively. On the other hand, its reaction with phenyl hydrazine gave the condensed product 1-[(anilinocarbothioyl)amino]-4-({aniline-2-phenylhydrazo-nomethyl}amino)benzene **11**.



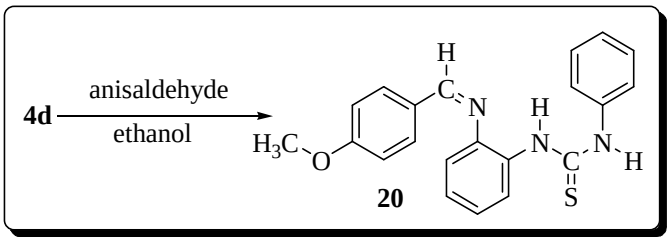
Reaction of **4b** with anisaldehyde gave 1-(4-(3-(4-methoxyphenyl)acryloyl)phenyl)-3-phenylthiourea **(12)** which can be used as key intermediate for the preparation of various new compounds through its reaction with hydrazine hydrate, hydroxylamine hydrochloride, ethyl cyanoacetate and malononitrile to give compounds **13-18**, respectively.



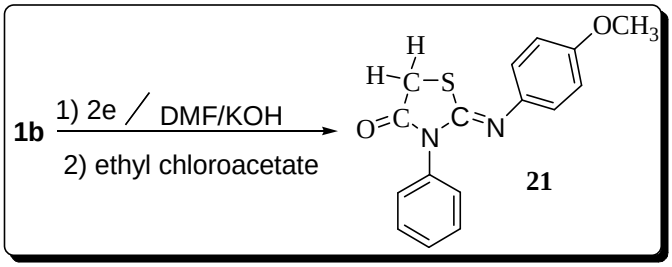
Reaction of **4e** with chloroacetic acid and aromatic aldehydes namely anisaldehyde, 2,4,6-trimethoxybenzaldehyde, 2,4-dihydroxybenzaldehyde, p-hydroxybenzaldehyde gave thiazolidin-4-ones **19a-d** in one pot reaction according to the following Scheme.



Condensation of **4d** with anisaldehyde in refluxing absolute ethanol gave compound **(20).**



On the other hand, reaction of phenylisothiocyanate **1b** with p-anisidine **2e** in DMF/KOH followed by treatment with ethyl chloroacetate afforded 2-(4-methoxyphenylimino)-3-phenylthiazolidin-4-one **(21).**



It was observed that microwave irradiation method was practically superior to conventional heating method in terms of higher yields, rapid and environmentally benign process. We carried out some of the reactions using microwave irradiation at 180 Watt to improve the yield and the time of the reactions. Synthesis of **3b**, **3e**, **4b** and **4e** under microwave irradiation showed observable improvement in the time of the reactions and slight improvement for the yields (Table 2). The reactions were carried out under solvent free conditions to avoid problems associated with solvent such as cost, handling and specifically safety, because of fire hazard due to occurrence of sparks in microwave ovens.

Table (2)

Compound No	Conventional method			Microwave method	
	Reaction conditions	Time(h)	Yield (%)	Time (min)	Yield (%)
3b	Stirring r.t in dry acetone	14	65	2	65
3e	Reflux in ethanol	6	60	2	63
4b	Stirring r.t in dry acetone	24	92	2	94
4e	Reflux in ethanol	6	90	2	90

3. Antimicrobial activity

The chemical samples were evaluated for their antimicrobial activity using the agar diffusion technique (Cooper 1972)**.** All chemical compounds were dissolved in dimethyl formamide DMF (5000 ppm). The bacteria and yeast were grown on nutrient agar medium.

The negative control was DMF showed no antimicrobial activity against the tested microorganisms.

All examinations were done in duplicates and the listed data are the average of the obtained results.

Table (3): Antimicrobial activity of the tested compounds against Gram +ve bacteria, Gram -ve bacteria and fungi.

Sample ID	Mean values of inhibition zones (in mm)					
	Gram +ve bacteria		Gram -ve bacteria		Fungi	
	Bacillus subtilis NCTC-10400	***Micrococcus luteus*** ATCC 25922	***Pseudomonas aeruginosa*** ATCC 10145	***Escherichia coli*** ATCC 23282	***Candida albicans*** IMRU 3669	***Aspergillus niger***
3c	**0.0**	**0.0**	**0.0**	**13.0**	**12.0**	**0.0**
4d	**0.0**	**0.0**	**0.0**	**13.0**	**12.0**	**12.0**
3b	**14.0**	**0.0**	**14.0**	**14.0**	**14.0**	**15.0**
4b	**0.0**	**0.0**	**0.0**	**12.0**	**0.0**	**0.0**
3e	**0.0**	**0.0**	**0.0**	**12.0**	**0.0**	**0.0**
4e	**0.0**	**0.0**	**0.0**	**13.0**	**0.0**	**0.0**
Ref.	**Erythromycin**				**Metronidazole**	
	34.0	**42.0**	**32.0**	**30.0**	**25.0**	**27.0**

From table (3), it was found that only compound **3b** possess antimicrobial activity against the tested Gram +ve bacterium Bacillus subtilis, while other tested compounds have no antimicrobial activity against the tested Gram

+ve bacteria.

Also, only compound **3b** showed antimicrobial activity against Gram -ve bacterium Psuedomonas aeruginosa, while all tested compounds showed moderate activity against the Escherichia coli bacterium.

On the other hand, compounds **3b**, **4b** and **3e** were found to possess weak antimicrobial activity towards the tested yeast Candida albicans, while compounds **4b** and **3e** were found to possess weak antimicrobial activity towards the tested fungus Aspergillus niger.

4. Experimental

Melting points were determined on an electrothermal (9100) apparatus and are uncorrected. I.R (ν in cm^{-1}) was measured in the Central laboratory of Ain Shams University. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer in DMSO-d_6 as solvent and TMS as internal standard in Cairo University and in Laboratoire Chimie et Procédés, DCSO, UMR 7652, Ecole Nationale Supérieure de Techniques Avancées (ENSTA), Paris, France, chemical shifts are quoted in δ(ppm). Mass spectra were recorded on a GC-MS 2010 Shimadzu in Cairo University. The microwave irradiation is carried out in Milestone, Microsynth. ACT36.

*3.1 General procedure for synthesis of compounds **3a,c-e; 4a,c-e;** and **5,6,7,8a,b***

A mixture of **1a, b** (0.01mol) and aromatic amines **2a,c-f** (0.01mol) in absolute ethanol (50 ml) was refluxed from 3-12h. The precipitated products obtained after cooling were filtered off and recrystallized from ethanol to give **3a,c-e; 4e,4e** and **8a,b**.

Table (4)

Compound No	Reaction Time (h)	Yield %	Compound No	Reaction Time (h)	Yield %
3a	12	42	**4d**	6	30
4a	10	36	**6**		50
7		50	**3e**	6	60
3c	6	40	**8a**	3	49
4c	6	45	**4e**	6	90
5		30	**8b**	3	70
3d	3	94			

*3.1.1 2-(3-Phenylureido) benzoic acid **3a***

White crystals, mp184°C, I.R: 1671(CO) , 3303-3332(NHs, OH) , ^{1}H-NMR:9.8 (s,2H,NH), 13.7 (s ,1H, OH) 7-8.4 (m ,9H, ArH), ^{13}C-NMR : 152(C=O) ketonic, 168(COOH), 115-142 (ArC). Anal. Calcd. for $C_{14}H_{12}N_2O_3$ (256.25): C, 65.62; H, 4.72; N, 10.93. Found: C, 65.74; H, 4.76; N, 11.13.

*3.1.2 1-(3-Aminopyridin-2-yl)-3-phenylurea **3c***

Reddish brown crystals, mp192°C, I.R:1627(CO),3180-3272(NH_2), 3473(NHs) ,^{1}H-NMR:8.7 (s ,2H , NH) 5.6 (d ,2H , NH_2) 6.5-7.8 (m ,8H, ArH), ^{13}C-NMR :152 (C=O), 112-142 (ArC). Anal. Calcd. for $C_{12}H_{12}N_4O$ (228.25): C, 63.15; H, 5.30; N, 24.55. Found: C, 62.93; H, 5.21; N, 24.73.

*3.1.3 1-(2-Aminophenyl)-3-phenylurea **3d***

White powder, mp 238-239°C, I.R:1693(CO), 3280(NH_2, NHs) broad band, MS: m/z, 227(M^{+}, 12.53%), 228(M+1, 4.52%), 134(100%). Anal. Calcd. for $C_{13}H_{13}N_3O$ (227.26): C, 68.70; H, 5.77; N, 18.49. Found: C, 68.61; H, 5.82; N, 18.64.

*3.1.4 1-(4-Methoxyphenyl)-3-phenylurea **3e***

Pink crystals, mp197-198° C, IR: 1634(CO), 3297(NHs), ^{1}H-NMR: 8.6 (s, 2H, NH), 6.8-7.4 (m, 9H, ArH), 3.8 (s, 3H, OCH_3), ^{13}C-NMR: 152 (C=O), 156 (ArC-OCH_3), 55 (OCH_3), 113-139 (ArC). Anal. Calcd. for $C_{14}H_{14}N_2O_2$ (242.27): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.62; H, 5.94; N, 11.72.

3.1.5 1,1'-(1,4-Phenylene)bis(3-phenylurea) ***8a***

Grey powder, mp>300°C, IR: 1633(CO), 3298(NHs), ^{1}H-NMR: 8.5 (s, 4H, NH) 6.9-7.4 (m, 14H, ArH), ^{13}C-NMR: 152(C=O), 118-139 (ArC). Anal. Calcd. for $C_{20}H_{18}N_4O_2$ (346.38): C, 69.35; H, 5.24; N, 16.17. Found: C, 69.52; H, 5.32; N, 15.93.

3.1.6 Compounds 4a and 7

The solid obtained after cooling was collected and recrystallized from ethanol to give **7**. Concentration of the filtrate and cooling gave solid identified as compound **4a**.

3.1.6.1 2-(3-Phenylthioureido)benzoic acid **4a**

White crystals, m.p 296-297°C, IR:1663(CO), 3220-3246(NHs,OH) , ^{1}H-NMR: 9.6-9.8 (s,2H,NH) , 13 (s,1H,OH) , 7.5-8.6 (m,9H, ArH) , MS: m/z, 272(M^{+}, 10.7%), 69(100%),.Anal. Calcd. for $C_{14}H_{12}N_2O_2S$ (272.32): C, 61.75; H, 4.44; N,10.29; S,11.77. Found: C, 61.58; H, 4.40; N, 10.12; S, 11.89.

3.1.6.2 2-(Phenylamino)-4H-benzo[d][1,3]oxazin-4-one ***7***

White powder, mp 218-220 °C, IR: 1685(CO), 1624(C=N), 3294(NHs), ^{1}H-NMR: 10.4 (s, 1H, NH), 7.4-8.3 (m, 9H, ArH), MS: m/z, 238(M^{+}, 31.1%), 239(M+1· 8.0%), 240(M+2, 2.8%), 146(100%). Anal. Calcd. for $C_{14}H_{10}N_2O_2$ (238.24):C, 70.58; H, 4.23; N, 11.76. Found: C, 70.44; H, 4.20; N, 11.67.

3.1.7 Compounds 4c and 5

The solid obtained after concentration and cooling was filtered off and separated manually. Crystallization of the buff crystals gave compound **4c** and the brown crystals gave compound **5**.

3.1.7.1 1-(3-Aminopyridin-2-yl)-3-phenylthiourea ***4c***

Buff crystals, mp156-157°C, IR: 3009-3034(NH_2), 3205(NHs), MS: m/z, 244(M^{+}, 20.91%), 61(100%). Anal. Calcd. for $C_{12}H_{12}N_4S$ (244.32): C, 58.99; H, 4.95; N, 22.93; S, 13.12. Found: C, 59.13; H, 4.83; N, 23.12; S, 12.84.

3.1.7.2 1,1'-(Pyridine-2,3-diyl)bis(3-phenylthiourea) ***5***

Brown crystals, mp>300 ^{o} C, IR: 3073(NHs), MS: m/z, 379(M^{+}, 11.3%), 380 (M+1, 8.7%), 381(M+2, 10.8%), 151(100%). Anal. Calcd. for $C_{19}H_{17}N_5S_2$ (379.09): C, 60.13; H, 4.52; N, 18.45; S, 16.90. Found: C, 59.88; H, 4.46; N, 18.45; S, 17.21.

3.1.8 Compounds 4d and 6

The solid obtained after concentration and cooling was filtered off. Boiling with benzene, the soluble part was identified as **4d**, the insoluble part as compound 6.

3.1.8.1 1-(2-Aminophenyl)-3-phenylthiourea ***4d***

Buff crystals, mp155-156° C, IR: 3009-3034(NH_2), 3205(NHs), ^{1}H-NMR: 9.8 (s, 2H, NH), 7.2-7.6 (m, 11H, ArH, NH_2), ^{13}C-NMR: 179 (C=S), 120-129(ArC). Anal. Calcd. for $C_{13}H_{13}N_3S$ (243.33): C,64.17 ; H, 5.39; N,17.27;S,13.18. Found: C, 63.89; H, 5.51; N, 17.48; S, 13.29.

3.1.8.2 1,1'-(1,2-Phenylene)bis(3-phenylthiourea) ***6***

Brown crystals, mp>300 °C, IR: 3154(NHs), MS: m/z, 378(M^{+}, 13.4%), 379(M+1, 9.8%), 150(100%). Anal. Calcd. for $C_{20}H_{18}N_4S_2$ (378.51):C, 63.46; H, 4.79; N, 14.80; S, 16.94. Found: C, 63.34; H, 4.71; N, 14.68; S, 17.12.

3.1.9 1-(4-Methoxyphenyl)-3-phenylthiourea ***4e***

Violet powder, mp187°C, IR: 3216(NHs), ^{1}H-NMR: 9.6 (s, 2H, NH), 6.9-7.5 (m, 9H, ArH), 3.7 (s, 3H, OCH_3), ^{13}C-NMR: 180(C=S), 55(OCH_3), 113-132(ArC). Anal. Calcd. for $C_{14}H_{14}N_2OS$ (258.34): C, 65.09; H, 5.46; N, 10.84; S, 12.41. Found: C, 65.21; H, 5.62; N, 10.93; S, 12.52.

3.1.10 1,1'-(1,4-Phenylene)bis(3-phenylthiourea) ***8b***

Grey powder, mp> 300°C, IR: 3209(NHs) , ^{1}H-NMR:9.8 (s , 4H,NH) , 7-7.5 (m,14H, ArH), ^{13}C-NMR: 179 (C=S), 123-139(ArC), MS: 243(10.84%), 135(53.47%) and 93(100%). Anal. Calcd. for $C_{20}H_{18}N_4S_2$ (378.51): C, 63.46; H, 4.79; N, 14.80; S, 16.94. Found: C, 63.61; H, 4.82; N, 14.95; S, 17.12.

3.1.11 Synthesis of 3b and 4b:

A mixture of p-aminoacetophenone **2b** (1.4g, 0.01mol), and **1a or 1b** (0.01mol) in dry acetone (50 ml) was stirred at r.t for 14 and 24h, respectively. The obtained product was filtered off and recrystallized from ethanol to

give 3b and 4b, respectively.

*3.1.11.1 1-(4-Acetylphenyl)-3-phenylurea **3b***

White crystals; yield 65%, mp 193-194°C, IR:1720(C=O), 1653(CO) , 3302(NHs), ^{1}H-NMR:9.1 & 8.8 (s, 2H , NH) 6.9-7.9 (m ,9H , ArH) ,2.5 (s ,3H, CH_3), ^{13}C-NMR : 152 (CONH), 190 ($COCH_3$), 26 (CH_3), 113-144 (ArC). Anal. Calcd. for $C_{15}H_{14}N_2O_2$ (254.28): C, 70.85; H, 5.55; N, 11.02. Found: C, 71.13; H, 5.62; N, 10.92.

*3.1.11.2 1-(4-Acetylphenyl)-3-phenylthiourea **4b***

White crystals; yield 92%, mp162-163°C, IR:1660(CO), 3293(NHs) , ^{1}H-NMR:10.1 (s,2H, NH), 7.1-7.9 (m,9H,ArH) , 3.3 (s,3H,CH_3), ^{13}C-NMR: 179(C=S), 190(CO), 26(CH_3), 122-144(ArC), MS: m/z, 270(M^{+} ,39.56%), 271(M+1 ,10.40%), 272 (M+2 ,3.04%),93(100%),. Anal. Calcd. for $C_{15}H_{14}N_2OS$ (270.35): C, 66.64; H, 5.22; N, 10.36; S, 11.86. Found: C, 66.72; H, 5.41; N, 10.39; S, 12.11.

*3.2 1-(4-(4,6-dioxo-3-phenyl-1,3-thiazinan-2-ylideneamino)phenyl)-3-phenylthiourea **9***

A mixture of **8b** (1.2g, 0.01mol) and diethyl malonate (1g, 0.01mol) was fused at 160°c for 6h. The product was filtered off and recrystallized from acetic acid to give dark orange powder; yield 62%, mp>300 °C, IR: 1641(CO), 1600(C=N) and 3264(NHs), MS: 311(20.77%), 135(18.53%) and 58(100%). Anal. Calcd. for $C_{23}H_{18}N_4O_2S_2$ (446.54):C, 61.86; H, 4.06; N, 12.55; S, 14.36. Found: C, 61.93; H, 4.19; N, 12.67; S, 14.21.

*3.3 Ethyl 2-(N-phenyl-N'-(4-(3-phenylthioureido)phenyl)carbamimidoylthio)acetate **10***

A mixture of **8b** (1.2g,0.01mol) and ethyl chloroacetate (0.65g,0.01mol) in DMF/K_2CO (30ml / 1gm) was stirred at r.t for 1 h then refluxed for 3h.The solution was poured onto crushed ice .The product was filtered off and recrystallized from ethanol. Brown powder; yield 60%, mp>300 °C, IR: 1723(CO), 1630(C=N), 3277(NHs), MS: 329(58%), 135(62%) and 77(100%). Anal. Calcd. for $C_{24}H_{24}N_4O_2S_2$ (464.6): C, 62.04; H, 5.21; N, 12.06; S, 13.80. Found: C, 62.18; H, 5.28; N, 12.30; S, 13.65.

*3.4 1-[(Anilinocarbothioyl)amino]-4-({aniline-2-phenylhydrazonomethyl}amino)benzene **11***

A mixture of **8b** (1.2g, 0.01mol) and phenyl hydrazine (0.54g, 0.01mol) in absolute ethanol (30 ml) was refluxed for 7h. The product separated during reflux was filtered off and recrystallized from ethanol. Brown powder; yield 85%, mp 210°C, IR: 1625(C=N), 3215(NHs), ^{13}C-NMR: 179(C= S), 123-139 (ArC), MS: 317(74.49%), 136(71.43%) and 92(100%). Anal. Calcd. for $C_{26}H_{24}N_6S$ (452.57): C, 69.00; H, 5.35; N, 18.57; S, 7.09 Found: C, 68.84; H, 5.46; N, 18.72; S,6.86.

*3.5 1-(4-(3-(4-Methoxyphenyl)acryloyl)phenyl)-3-phenylthiourea **12***

A mixture of **4b** (2.7g, 0.01mol) and anisaldehyde (1.56g, 0.01 mol) in alc.NaOH (NaOH 0.5 g in methanol 50 ml), was stirred at r.t for 8h. The precipitated product was filtered off and recrystallized from ethanol. Yellow powder; yield 85%, mp185-187 °C, IR:1660(CO), 3289(NHs), ^{1}H-NMR: 10.1 (s, 2H, NH) 7.1-7.6 (m,15H, ArH, CH=CH) , 3.3 (s, 3H, OCH_3), ^{13}C-NMR: 196(C=O), 178(C=S) , 121-139(ArC), 20 (CH_3), MS: m/z, 388(M^{+}, 31.6%), 63(100%). Anal. Calcd. for $C_{23}H_{20}N_2O_2S$(388.48):C, 71.11; H, 5.19; N, 7.21; S, 8.25. Found: C, 71.03; H, 5.21; N, 7.14; S, 8.41.

*3.6 1-(4-(1-Acetyl-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)-3-phenylthiourea **13***

A mixture of **12** (1g, 0.0025mol) and hydrazine hydrate (0.51g, 0.016mol) in acetic acid (20 ml) was refluxed for 5 h. The precipitated product was purified by recrystallization from ethanol. Yellowish brown powder; yield 50%, mp>300°C, IR: 3273(NHs), 1671(CO), MS: m/z, 444 (M^{+}, 17.4%), 445(M+1, 12.9%), 120(100%). Anal. Calcd. for $C_{25}H_{24}N_4O_2S$ (444.55):C, 67.54; H, 5.44; N, 12.60; S, 7.21. Found: C, 67.38; H, 5.43; N, 12.52; S, 7.36.

*3.7 1-(4-(5-(4-Methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)-3-phenylthiourea **14***

A mixture of **12** (1g, 0.0025mol) and hydrazine hydrate (0.51g, 0.016mol) in absolute ethanol (50 ml) was refluxed for 4 h. The precipitated product was purified by recrystallization from ethanol. Yellowish green crystals; yield 56%, mp142-144°C, IR: 3177, 3285(NHs), 1635(C=N) , ^{1}H-NMR: 6.5 (s ,2H , NH) , 7.6-7.9 (m,13H , ArH) , 9.1 (s, 1H , NH) , 5 (m,3H , CH_2,CH), 3.5(s, 3H, OCH_3), ^{13}C-NMR: 178(C=S), 122-142 (ArC), 11 (CH_3), 40 (CH_2,CH), MS: m/z, 402(M^{+}, 57.3%), 403(M+1 , 52.7%), 404(M+2, 50.0%),105(100%).Anal. Calcd. for $C_{23}H_{22}N_4OS$ (402.51):C, 68.63; H, 5.51; N, 13.92; S, 7.97. Found: C, 68.48; H, 5.44; N, 13.76; S, 8.20.

*3.8 1-(4-(5-(4-Methoxyphenyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-phenylthiourea **15***

A mixture of **12** (1g, 0.0025mol) and hydroxylamine hydrochloride (1gm, 0.014mol) in dry pyridine (15ml) was refluxed on water bath for 8 h. The solution was poured onto crushed ice/HCl .The product was filtered off and recrystallized from ethanol. Grey crystals; yield 40%, mp120-122°C, IR: 3195(NHs), 1664(C=N), MS: m/z,

403(M^{+}, 64.0%), 404(M+1, 82.0%), 149(100%).Anal. Calcd. for $C_{23}H_{21}N_3O_2S$ (403.5): C, 68.46; H, 5.25; N, 10.41; S, 7.95. Found: C, 68.35; H, 5.20; N, 10.04; S, 8.16.

3.9 1-(4-(5-Cyano-6-hydroxy-4-(4-methoxyphenyl)-4H-pyran-2-yl)phenyl)-3-phenylthiourea ***16***

A mixture of **12** (2g, 0.005mol) and ethyl cyanoacetate(0.6g, 0.005mol) in sodium ethoxide (Na 0.25g in absolute ethanol 50ml). The reaction mixture was fused at 160°C for 5h. The product was purified by recrystallization from ethanol. Yellowish brown powder; yield 25%, mp 171-174 °C, IR: 3348(NHs, OH) broad band, 2186(C≡N), MS: m/z, 455(M^{+}, 15.1%), 118(100%).Anal. Calcd. for $C_{26}H_{21}N_3O_3S$(455.53): C, 68.55; H, 4.65; N, 9.22; S, 7.04. Found: C, 68.41; H, 4.60; N, 9.11; S, 6.91.

3.10 1-(4-(4,4-Dicyano-3-(4-methoxyphenyl)butanoyl)phenyl)-3-phenylthiourea ***17***

A mixture of **12** (4g, 0.01 mol) and malononitrile (0.7g, 0.01mol) in absolute ethanol (50 ml) and few drops of piperidine was refluxed for 19 h. The product was filtered off and recrystallized from ethanol. Pale brown powder; yield 80%, mp>300°C, IR: 3321, 3208(NHs), 2208(C≡N), 1678(CO), MS: m/z, 454 (M^{+}, 7.6%), 455 (M+1, 52.5%), 264 (100%).Anal. Calcd. for $C_{26}H_{22}N_4O_2S$ (454.54): C, 68.70; H, 4.88; N, 12.33; S, 7.05. Found: C, 68.58; H, 4.83; N, 12.17; S, 7.22.

3.11 1-(4-(6-Amino-5-cyano-4-(4-methoxyphenyl)-4H-pyran-2-phenyl)-3-phenylthiourea ***18***

A mixture of **12** (2g, 0.005 mol) and malononitrile (0.7g, 0.01mol) in sodium ethoxide (Na 0.25g in absolute ethanol 1ml) was fused at 160°c for 5h. The product was purified by recrystalization from ethanol. Reddish brown powder; yield 35%, mp>300 °C, IR: 3334 (NH_2, NHs) broad band, 2204(C≡N), MS: m/z, 454 (M^{+}, 23.0%), 455(M+1, 25.2%), 80(100%).Anal. Calcd. for $C_{26}H_{22}N_4O_2S$ (454.54): C, 68.70; H, 4.88; N, 12.33; S, 7.05. Found: C, 67.71; H, 4.85; N, 12.0; S, 6.81.

3.12 General procedure for synthesis of compounds ***19a-d***

A mixture of **4e** (2.6g, 0.01mol), chloroacetic acid (1g, 0.01mol), and aromatic aldehydes

(0.01mol) was refluxed in absolute ethanol (50ml). The precipitated products obtained were filtered off and recrystallized from ethanol.

Table (5)

Compound No	Reaction time(h)	Yield %
19a	8	80
19b	26	74
19c	17	75
19d	29	78

3.12.1 5-(4-Methoxybenzylidene)-3-(4-methoxyphenyl)-2-(phenylimino)thiazolidin-4-one ***19a***

Green crystals; yield 83%, mp197-199 °C, IR: 1708(CO), MS: m/z, 416(M^{+}, 18.1%), 417(M+1, 5.4%), 164(100%). Anal. Calcd. for $C_{24}H_{20}N_2O_3S$ (416.49): C, 69.21; H, 4.84; N, 6.73; S, 7.70. Found: C, 69.09; H, 4.81; N, 6.67; S, 7.83.

3.12.2 5-(2,4,6-Trimethoxybenzylidene)-3-(4-methoxyphenyl)-2-(phenylimino)thiazolidin-4-one ***19b***

Green powder; yield 74%, mp 211-212 °C, IR: 1705(CO), MS: m/z, 476(M^{+}, 20%), 477(M+1, 23.1%), 478(M+2 , 27.3%), 69(100%).Anal. Calcd. for $C_{26}H_{24}N_2O_5S$ (476.54): C, 65.53; H, 5.08; N, 5.88; S, 6.73. Found: C, 65.44; H, 4.97; N, 5.79; S, 6.91.

3.12.3 5-(2,4-Dihydroxybenzylidene)-3-(4-methoxyphenyl)-2-(phenylimino)thiazolidin-4-one ***19c***

Green powder; yield 75%, mp 178-179°C, IR: 1644(CO), 3386(OHs); MS: m/z, 418(M^{+}, 11.1%), 419 (M+1, 17.9%), 420 (M+2, 9.59%), 243(100%). Anal. Calcd. for $C_{23}H_{18}N_2O_4S$ (418.47): C, 66.01; H, 4.34; N, 6.69; S, 7.66. Found: C, 65.87; H, 4.30; N, 6.62; S, 7.82.

3.12.4 5-(4-Hydroxybenzylidene)-3-(4-methoxyphenyl)-2-(phenylimino)thiazolidin-4-one ***19d***

Green crystals; yield 78%, mp 253-255°C, IR: 1690(CO), 3326 (OH), ^{1}H-NMR: 10.2 (s, 1H, OH) 7.2-7.8 (m, 14H, ArH,C=CH), 3.8 (s,3H, OCH_3).Anal. Calcd. for $C_{23}H_{18}N_2O_3S$ (402.47): C, 68.64; H, 4.51; N, 6.96; S, 7.97. Found: C, 68.54; H, 4.47; N, 6.88; S, 8.30.

3.13 1-(2-(4-Methoxybenzylideneamino)phenyl)-3-phenylthiourea ***20***

A mixture of **4d** (2.43g, 0.01mol) and anisaldehyde (1.56g, 0.01mol) in absolute ethanol (50 ml) was refluxed on water bath for 3h. The product was purified by recrystallization from ethanol. Buff crystals; yield 35%, mp>300°C, IR: 1620(C=N), 3154(NHs), MS: m/z, 361($M^{\cdot+}$, 49.1%), 362(M+1, 42.8%), 150(100%). Anal. Calcd. for $C_{21}H_{19}N_3OS$ (361.46):C, 69.78; H, 5.30; N, 11.63; S, 8.87. Found: C, 69.64; H, 5.30; N, 11.44; S, 8.72.

*3.14 2-(4-Methoxyphenylimino)-3-phenylthiazolidin-4-one **21***

A mixture of **1b**(2.7g,0.02mol) and p-anisidine **2e** (1.3g,0.01mol) in DMF/KOH (20ml/1.12g) was stirred overnight at r.t , and then ethyl chloroacetate (2.44g,0.02mol) was added and stirring was continued for 24h. The solid obtained after pouring onto crushed ice/HCl was filtered off and recrystallized from benzene. White powder; yield 25%, mp 166-168°C, I.R: 1724(CO), 1636(C=N), MS: m/z, 298(M^{+}, 9.3 %), 299(M+1, 3.0%), 300(M+2, 2.7%), 77(100%).Anal. Calcd. for $C_{16}H_{14}N_2O_2S$ (298.36): C, 64.41; H, 4.73; N, 9.39; S, 10.75. Found: C, 64.32; H, 4.71; N, 9.23; S, 10.90.

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